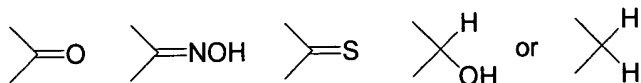


2. Please delete the paragraph beginning on page 12, line 1 and ending on page 12, line 3.

3. Please replace the original paragraph beginning on page 12, line 8 and ending on page 12, line 10 with the following rewritten paragraph:

A2

In the generalized formula (L), D represents



4. Please replace the original paragraph beginning on page 12, line 20 and ending on page 12, line 21 with the following rewritten paragraph:

A3

Each group  $R^6$  is alkyl, alkenyl, alkynyl, heteroaryl, non-aromatic cyclic, and combinations thereof optionally substituted with one or more heteroatoms.

5. Please replace the paragraph beginning on page 13, line 1, and ending on page 13, line 2 with the following rewritten paragraph:

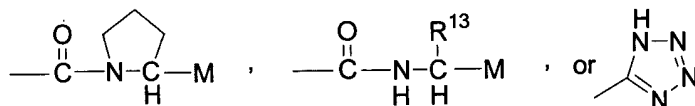
A4

In the generalized formula (L), E preferably represents a linear or cyclic alkyl moiety substituted with a mono- or bi-heterocyclic ring structure.

6. Please replace the paragraph beginning on page 13, line 3 and ending on page 13, line 7 with the following rewritten paragraph:

A5

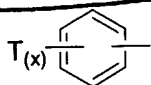
In the generalized formula (L), G represents  $-\text{PO}_3\text{H}_2$ ,  $-\text{M}$ ,



in which M represents  $-\text{CO}_2\text{H}$ ,  $-\text{CON}(\text{R}^{11})_2$  wherein  $\text{R}^{11}$  is H or simple alkyl, or  $-\text{CO}_2\text{R}^{12}$  wherein  $\text{R}^{12}$  is lower alkyl, and  $\text{R}^{13}$  represents any of the side chains of the 19 noncyclic naturally occurring amino acids.

7. Please replace the chemical structure at page 14, line 12 with the following rewritten structure and accompanying text:

A 6



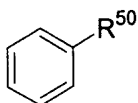
in which  $R^1$  represents H or alkyl of 1 - 3 carbons.

8. Please delete the paragraph beginning at page 14, line 13 and ending at page 15, line 3.

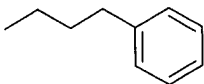
9. Please delete original page 15 and replace it with the following rewritten page 15:

A 7

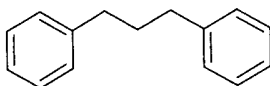
Throughout this application, in the displayed chemical structures, an open bond indicates the point at which the structure joins to another group. For example,



where  $R^{50}$  is



is the structure

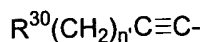


In the above structures for  $(T)_x A$ , the aromatic ring is referred to as the A ring or A unit, and T represents a substituent group, referred to as a T group or T unit. x is preferably 1.

10. Please delete original page 16 and replace it with the following rewritten page 16:

A 8

The substituent group T can be an acetylene containing moiety with the general formula:



where  $n'$  is 1-4 and  $R^{30}$  is selected from the group consisting of: HO-, MeO-, N(n-Pr)<sub>2</sub>-, CH<sub>3</sub>CO<sub>2</sub>-, CH<sub>3</sub>CH<sub>2</sub>OCO<sub>2</sub>-, HO<sub>2</sub>C-, OHC-, Ph-, 3-HO-Ph-, and PhCH<sub>2</sub>O-, provided that when  $R^{30}$  is Ph or 3-HO-Ph,  $n' = 0$ .

The B ring of generalized formula (L) is a substituted or unsubstituted aromatic or heteroaromatic ring, in which any substituents are groups which do not cause the molecule to fail to fit the active site of the target enzyme, or disrupt the relative conformations of the A and B rings, such that they would be detrimental. Such substituents may be moieties such as lower alkyl, lower alkoxy, CN, NO<sub>2</sub>, halogen, etc., but are not to be limited to such groups.

Chemical structures of five five-membered aromatic heterocycles: thiophene, furan, pyrrole, selenophene, and silole. Each structure is shown with a central atom (S, O, or Se) and two methyl groups attached to the ring.

- A 9

$$R^{15} \left( \text{---} \right)_{r'} Z - CH_2 -$$

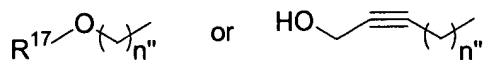
A 10

AT

- $$R^{33}(CH_2)_b-C\equiv C-$$

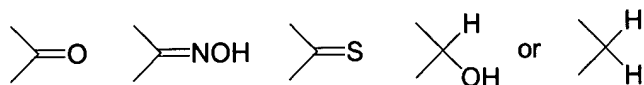
4

R<sup>15</sup> may also be H, Cl, MeO or

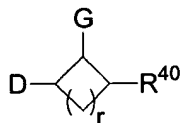


wherein n'' is 0-4, R<sup>17</sup> is C<sub>2</sub>H<sub>5</sub>, allyl, or benzyl.

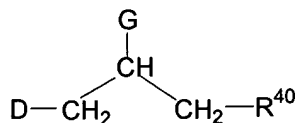
In the generalized formula (L), D represents the moieties:



In the generalized formula (L), E represents the moiety between D and G shown by the following formula:



wherein r is 0-2 and R<sup>40</sup> is a mono- or bi- heterocyclic structure. When r=0 the above structure takes the form



When r is 1 or 2, a cyclobutyl or cyclopentyl ring is formed, respectively. Each ring of the mono- or bi- heterocyclic structures comprise 5-7 membered rings substituted with 1-3 heteroatoms independently selected from N, S, and O; one or two carbons of the ring are optionally carbonyl carbons; any sulfur of the ring is optionally -S(O)- or -S(O)<sub>2</sub>-; one or more ring members are optionally substituted with one or two methyl groups.

14. Please delete original page 19 and replace it with the following rewritten page 19:

In addition, aryl or heteroaryl portions of any of the T or R<sup>6</sup> groups optionally may bear up to two substituents such as -(CH<sub>2</sub>)<sub>y</sub>C(CR<sup>11</sup>)(R<sup>12</sup>)OH, -(CH<sub>2</sub>)<sub>y</sub>OR<sup>11</sup>, -(CH<sub>2</sub>)<sub>y</sub>SR<sup>11</sup>, -(CH<sub>2</sub>)<sub>y</sub>S(O)R<sup>11</sup>, -(CH<sub>2</sub>)<sub>y</sub>S(O)<sub>2</sub>R<sup>11</sup>, -(CH<sub>2</sub>)<sub>y</sub>SO<sub>2</sub>N(R<sup>11</sup>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>y</sub>N(R<sup>11</sup>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>y</sub>N(R<sup>11</sup>)COR<sup>12</sup>, -OC(R<sup>11</sup>)<sub>2</sub>O- in which both oxygen atoms are connected to the aryl ring.

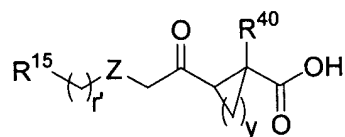
15. Please delete original page 21 and replace it with the following rewritten page 21:

It is to be understood that as used herein, the term "alkyl" means straight, branched, cyclic, and polycyclic materials. The term "haloalkyl" means partially or fully halogenated alkyl

groups such as  $-(CH_2)_2Cl$ ,  $-CF_3$  and  $-C_6F_{13}$ , for example.

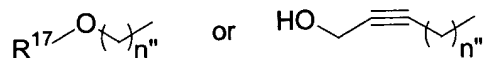
In the generalized formula (L), the A and B rings are preferably phenyl and phenylene, respectively, the A ring preferably bears at least one substituent group T preferably located on the position furthest from the position of the A ring which is connected to the B ring, the D unit is preferably a carbonyl group, and the G unit is preferably a carboxyl group.

Certain alternative embodiments include compounds having matrix metalloproteinase inhibitory activity and the following generalized formula:



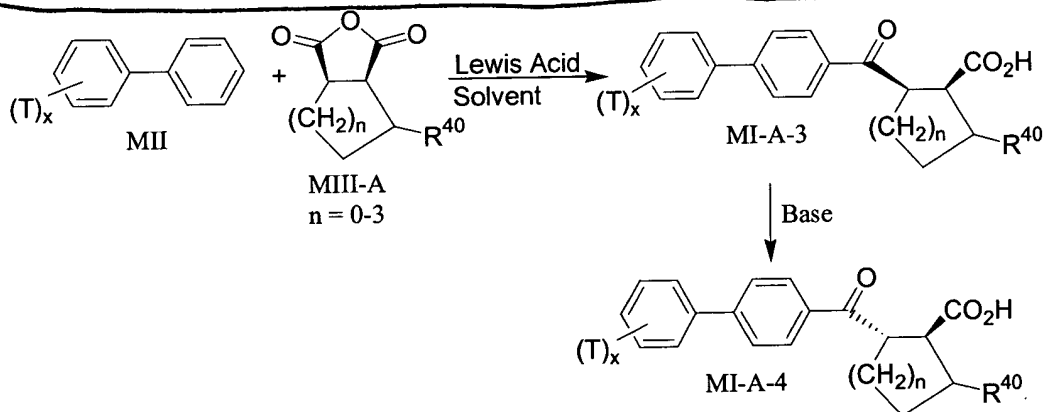
where  $Z = (CH_2)_e-C_6H_4-(CH_2)_f$  or  $(CH_2)_g$ ,  $e = 0-8$ ,  $f = 0-5$ ,  $g = 0-14$ ,  $r'$  is  $0-6$  and where  $y$  is  $0, 2$ , or  $3$ .

$R^{15}$  may be H, Cl, MeO or



wherein  $n''$  is  $0-4$ ,  $R^{17}$  is  $C_2H_5$ , allyl or benzyl, and  $R^{40}$  is one of:

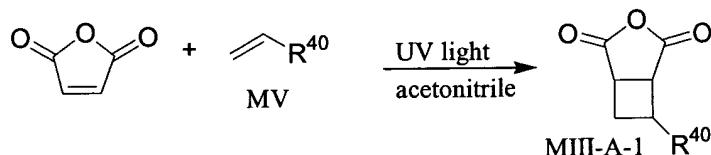
16. Please replace the original chemical equation beginning on page 28, line 10 and ending on page 28, line 17 with the following rewritten chemical equation:



17. Please delete the original paragraph beginning on page 28, line 18 and ending on page 29, line 9, and replace this paragraph and the accompanying chemical equation on page 29, lines 7-9 with the following rewritten material:

A 15

Method A is especially useful for the preparation of cyclic compounds such as MI-A-3, in which two  $R^6$  groups are connected in a methylene chain to form a 3-7 member ring. Small ring (3-5 member) anhydrides are readily available only as cis isomers which yield cis invention compounds MI-A-3. The trans compounds MI-A-4 are then prepared by treatment of MI-A-3 with a base such as DBU in THF. The substituted four member ring starting material anhydrides such as MIII-A-1 are formed in a photochemical 2+2 reaction as shown below. This method is especially useful for the preparation of compounds in which  $R^{40}$  is acetoxy or acetoxymethylene. After the subsequent Friedel-Crafts reaction the acetate can be removed by basic hydrolysis and the carboxyl protected by conversion to 2-(trimethylsilyl)ethyl ester. The resultant intermediate with  $R^{40} = CH_2OH$  can be converted to invention compounds with other  $R^{40}$  groups by using procedures described in General Method G.



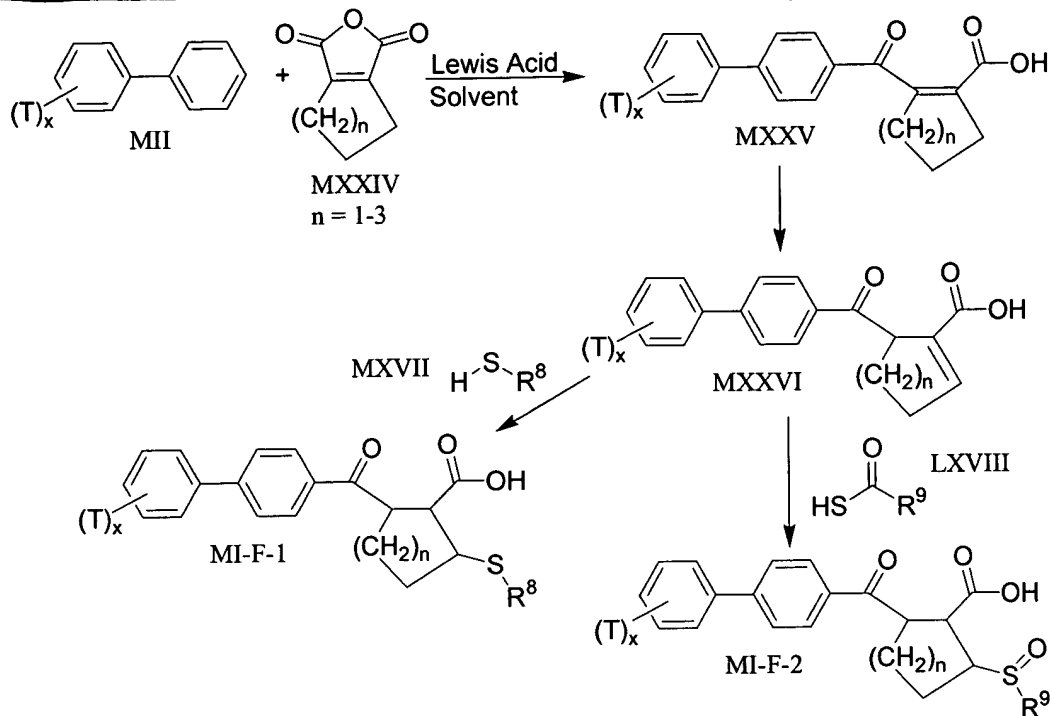
18. Please delete the original paragraph beginning on page 30, line 7 and ending on page 30, line 9 with the following rewritten paragraph:

A 16

Alternatively, a diester intermediate MIX, which contains  $R^{12} = \text{allyl}$ , can be exposed to Pd catalysts in the presence of pyrrolidine to yield MI-B-2 ( $R^{12} = H$ ) (Dezeil, Tetrahedron Lett. 28, 4371, 1990).

19. Please delete the original reaction scheme beginning on page 36, line 2 and ending on page 36, line 12 and replace it with the following rewritten reaction scheme:

A 17



20. Please delete the original paragraph beginning on page 39, line 3 and ending on page 39, line 9 and replace it with the following rewritten paragraph:

A 18

**General Method I** - The compounds of this invention in which (T)<sub>x</sub> is an alkynyl or substituted alkynyl are prepared according to general method I (Austin, J. Org. Chem. 46, 2280 (1981)). Intermediate MX is prepared according to methods A, B, C, D or G by starting with commercial MII (T = Br). Reaction of MX with substituted acetylene MXI in the presence of Cu(I) / palladate reagent gives invention compound MI-I-1. In certain cases, R<sup>3</sup> may be an alcohol blocked as trialkylsilyl. In such cases the silyl group can be removed by treatment with acids such as trifluoroacetic acid or HF - pyridine reagent.

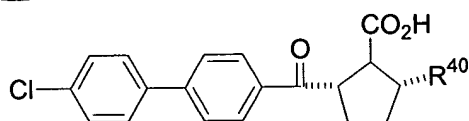
21. Please delete the original paragraph beginning on page 46, line 1 and ending on page 46, line 9 and replace it with the following rewritten paragraph:

A 19

**Step 1.** A solution of exo-oxobicyclo [2.2.1]heptane-7-carboxylic acid (prepared using the protocols described in Tetrahedron, 37, suppl., 411, 1981) (3.04g. 19.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (45 mL) was cooled to 0°C and treated with 2-(trimethylsilyl) ethanol (2.7 mL, 18.6 mmol), EDC

(3.94 g, 20.55 mmol) and DMAP (0.11 g, 0.9 mmol). After warming to room temperature and stirring for 2 hrs., the reaction mixture was quenched with water and diluted with CH<sub>2</sub>Cl<sub>2</sub>. After separating the layers, the organic phase was washed with satd. aq. NaCl, dried over MgSO<sub>4</sub> and concentrated. Purification by MPLC (0-25% EtOAc-hexanes) provided the target compound (3.9 g, 78%) as a colorless oil. <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ 4.18 (m, 2H), 2.88 (m, 2H), 2.76 (m, 1H), 2.05 (m, 4H), 1.50 (m, 2H), 0.99 (t, J = 8.4Hz, 2H), 0.99 (s, 9H).

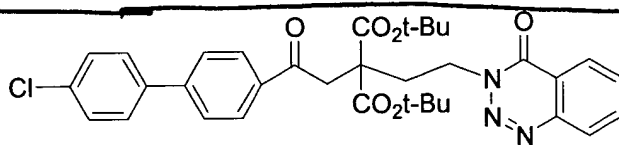
22. Please delete the original chemical structure shown on page 53, line 3 (first structure, between the title of the table and the table) and replace it with the following rewritten structure:



23. Please delete the first row of Table 1, page 53, line 4, and replace it with the following rewritten first row of column headings:

Example	R <sup>40</sup>	Isomer	Characterization
---------	-----------------	--------	------------------

24. Please delete the original chemical structure shown on page 59, line 15, and replace it with the following rewritten chemical structure:



25. Please delete the title and first row of the original table on page 67, beginning at line 9 and ending at line 10, and replace with the following rewritten title and row of column headings:

Table 2

Example	MMP-3 Fluorogenic IC <sub>50</sub> nM	MMP-9 Fluorogenic IC <sub>50</sub> nM	MMP-2 Fluorogenic IC <sub>50</sub> nM
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